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TITLE: "Olfactory Deficits in MCI as Predictor of Improved Cognition on Donepezil"

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<b>13. SUPPLEMENTARY NOTES</b>					
<b>14. ABSTRACT</b> Background. A large proportion of patients with amnesic mild cognitive impairment (MCI) convert to Alzheimer's disease (AD) and hence acetylcholinesterase inhibitors (AChEI) are commonly prescribed in patients with MCI though it is not FDA approved for this condition. Therefore, predicting which MCI patients are likely to improve cognitively with AChEI treatment is important. Hypotheses. 1. The acute decrease in UPSIT (Odor identification test) scores from pre- to post- atropine nasal spray challenge conducted at baseline (0 weeks) will be associated with cognitive improvement (SRT total recall and modified ADAS-cog) from baseline to 26 weeks and 52 weeks of donepezil treatment. 2. Increase in UPSIT scores from baseline to 8 weeks of donepezil treatment will be associated with cognitive improvement from baseline to 26 and 52 weeks. Exploratory Hypothesis. The acute atropine-induced decrease in UPSIT scores, and increase in UPSIT scores from baseline to 8 weeks, will be associated with a decreased likelihood of conversion to dementia at 52 weeks. Study Design. In this proof of concept study, 60 patients with mild cognitive impairment will be treated openly with donepezil 5 to 10 mg per day and followed for 52 weeks (one year), with an atropine challenge test also conducted at baseline.					
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**INTRODUCTION:** Individuals with cognitive deficits, whether due to traumatic brain injury or due to mild cognitive impairment, may improve with donepezil treatment. Olfactory identification deficits may be an early test that can identify who in the high-risk population is most likely to develop dementia and therefore identifies patients for early interventions. Based on the study results, the presence of olfactory identification deficits can be used to decide if the patient should receive treatment with a cholinesterase inhibitor like donepezil.

**BODY:** 168 patients have been screened for this protocol. 41 patients have been recruited. 4 patients never began the study, 2 patients chose to dropout of the study, 21 patients have completed the study, and 14 patients are currently participating in the study. Of the 35 active patients and completers, 16 are female and 19 are male. The mean age of the patients is 71.15 years, standard deviation 9.90.

All active patients and completers have been given baseline pre and post atropine spray UPSITs, have completed all procedures according to the protocol schedule, and have been treated with either 5mg or 10mg Donepezil daily. Of the active patients and completers, 10 patients could not tolerate donepezil 5 mg daily. For clinical reasons, they were started on a comparable cholinesterase inhibitor, galantamine or rivastigmine, and are being followed at the scheduled time-points as per the intent-to-treat principle employed in this study. The data obtained will be analyzed in two ways: in primary analyses we will count donepezil dropouts with subsequent time-point assessments handled as planned originally under the intent-to-treat principle, and in secondary analyses we will combine the data in patients who receive donepezil or galantamine or rivastigmine since they are all cholinesterase inhibitors with very similar effects on cognition and function (and we will include all assessments under the intent-to-treat principle). This change was approved by the NYSPI/Columbia local IRB and also approved by the DoD regulatory authorities.

There have been two adverse events to date, neither of which was rated as being related to study medication.

1. A patient was admitted to the hospital for 4 weeks for neglecting to take his psychiatric medications and alcohol abuse. He was released, now has a well-defined psychosocial support team involved in his care, and has completed our study.
2. A patient began seeking treatment for urinary symptoms and was diagnosed with cancer in his left kidney with accompanying bladder involvement. He received focused beam radiation, and reported at his most recent clinic visit that he felt fine and considered himself lucky that the cancer was caught and treated as efficiently as it was. He has since completed our study.

Intranasal Atropine has been administered to 37 subjects. For the last 29 subjects, we used the “squirt system”, developed by Scheibe & colleagues in 2008. The squirt system includes a 2 cm sterile plastic tube attached to a one cc syringe. The syringe is filled with 0.1 cc of atropine and then the tube is placed in the nasal cavity parallel to the nasal septum, and directed at the nasal cleft (back and up towards the cribriform plate). The atropine is then squirted up towards the superior turbinate bone in the nose. This is immediately followed by the standard 1 minute Mecca position, 45 minute delay, and repeat UPSIT test, as before. The squirt system has been producing consistent results. In September 2013, we submitted the “Atropine Nasal Spray for Olfactory Challenge in Humans” to the Militarily-Relevant, Peer Reviewed Alzheimer’s

Disease Program's (MRPRA) "Product Database".

From a data analytic standpoint, we will first include all subjects in evaluating the change in UPSIT from pre- to post-atropine spray as a predictor of donepezil treatment response, and then separately assess the impact of the first 8 subjects where different techniques were used as noted above. We will include and then exclude the subset of the first 8 patients in statistical analyses and then assess if the results change. Of note, the atropine challenge-induced change in UPSIT scores represents the first of the two main hypotheses; the second hypothesis pertaining to change in UPSIT scores from baseline to 8 weeks as a predictor of longer-term donepezil response is unaffected by the change in the atropine spray challenge procedure.

**KEY RESEARCH ACCOMPLISHMENTS:** No presentations or publications to date from this study.

**REPORTABLE OUTCOMES:** None; study is not yet complete.

## CONCLUSIONS

Recruitment for this study was ended on March 31, 2015. Until this date, we had been actively recruiting for this study from the sources described in the original grant application. The study will now enter a one year, no cost extension (NCE) period, during which time no new participants will be recruited and all active patients will be followed at their scheduled time-points until they have concluded the protocol. This NCE period will end on April 1, 2016.

## REFERENCES:

Scheibe M, Bethge C, Witt M, Hummel T. Intranasal administration of drugs. Arch Otolaryngol Head Neck Surg. 2008 Jun;134(6):643-6. doi: 10.1001/archotol.134.6.643.

## APPENDICES:

None.